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NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing.

Bibliographic Source(s)

Hershfield MS, Callaghan JT, Tassaneeyakul W, Mushiroda T, Thorn CF, Klein TE, Lee MT. Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. Clin Pharmacol Ther. 2013 Feb;93(2):153-8. [40 references] PubMed

Guideline Status

This is the current release of the guideline.

The guideline developer reaffirmed this guideline in 2015.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Therapeutic Recommendations

The Taiwan Department of Health has updated the labeling for allopurinol to include information on *human leukocyte antigen B (HLA-B)*58:01* (http://www.doh.gov.tw/EN2006/Newsroom/Press_list.aspx?year=2009&doc_no=72847). The updated label describes the strong association between *HLA-B*58:01* and allopurinol-induced Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in the Han-Chinese population and recommends testing for the allele before the use of allopurinol. The updated label does not recommend such testing for patients who have had no adverse events after prolonged use of allopurinol. At the time of writing this article, the U.S. Food and Drug Administration (FDA) had not updated the labeling for allopurinol. However, given the high specificity for allopurinol-induced severe cutaneous adverse reactions (SCAR), allopurinol should not be prescribed to patients who have tested positive for *HLA-B*58:01*. Alternative medication should be considered for these patients to avoid the risk of developing SCAR. For patients who have tested negative, allopurinol may be prescribed as usual (see the table below). However, testing negative for *HLA-B*58:01* does not totally eliminate the possibility of developing SCAR, especially in the European population.

Several clinical factors have been reported to be associated with an increased risk for allopurinol hypersensitivity. Renal dysfunction is the most significant nongenetic factor, and patients with renal insufficiency were four times more likely to develop adverse events than those with normal

renal function. The risk of allopurinol-induced hypersensitivity is also reported to increase with the concomitant use of ampicillin or amoxicillin.

In addition to SCAR, allopurinol therapy is also associated with a 2%–3% incidence of less severe rashes unassociated with systemic symptoms or organ damage. FDA guidelines recommend discontinuing allopurinol if a rash develops. Until recently, only uricosuric drugs such as probenecid and benzbromarone were available for the patients who need to discontinue allopurinol due to skin rash. However, probenecid is often less effective than allopurinol, particularly in patients with renal insufficiency, and benzbromarone is not an approved drug in many countries. This has prompted attempts to induce tolerance to allopurinol by rechallenge with gradual escalation of low doses as tolerated. This unreliable approach has not been widely accepted, and its use may decline because alternative urate-lowering therapies are now available. Febuxostat, which received FDA approval in 2009, is available in 19 countries. It is a nonpurine xanthine oxidase inhibitor that is primarily metabolized in the liver to inactive glucuronide and excreted into the urine and bile. Therefore, mild to moderate renal impairment might have little impact on the pharmacokinetics of febuxostat. It was reported to be tolerated in 12 of 13 patients with a history of severe allopurinol hypersensitivity. In 2010, the FDA approved pegloticase, a PEGylated urate oxidase, as an orphan drug for treating patients with refractory chronic gout who had an inadequate response to, or were intolerant of, other urate-lowering drugs. Newer urate-lowering drugs are in clinical trials.

Table. Recommended Therapeutic Use of Allopurinol by *Human Leukocyte Antigen (HLA)-B* Genotype

Genotype	Implications for Phenotypic Measures	Recommendations for Allopurinol	Classification of Recommendations
Noncarrier of *HLA-B*58:01* (*X/*X)[a]	Low or reduced risk of allopurinol-induced SCAR	Use allopurinol per standard dosing guidelines	Strong
Carrier of HLA-B*58:01 (*HLA-B*58:01*/*X,[a] *HLA-B*58:01/HLA-B*58:01*)	Significantly increased risk of allopurinol-induced SCAR	Allopurinol is contraindicated	Strong

HLA-B, human leukocyte antigen-B; SCAR, severe cutaneous adverse reaction.

[a]*HLA-B* genotype other than *HLA-B*58:01* is indicated by *X.

Definitions:

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Hyperuricemia and gout

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Medical Genetics

Pharmacology

Preventive Medicine

Rheumatology

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide pharmacogenetic information relevant to the clinical use of *human leukocyte antigen B (HLA-B)*58:01* genotyping results in patients with indications for allopurinol use

Target Population

Individuals with hyperuricemia or gout

Interventions and Practices Considered

Allopurinol therapy based on *human leukocyte antigen B (HLA-B)*58:01* genotype

Major Outcomes Considered

- Risk of allopurinol-induced severe cutaneous adverse reaction (SCAR)
- Risk of allopurinol-induced Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)
- Risk of allopurinol-induced hypersensitivity
- Other adverse effects of allopurinol
- Positive and negative predictive value of *human leukocyte antigen B (HLA-B)*58:01* testing

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

2013 Guideline

The guideline authors searched the PubMed database (1966 to October 2011) for keywords ((HLA OR HLA-B OR HLA-B58 OR HLA-B*58:01) AND (allopurinol)), and retrieved fifty articles. Of those fifty the majority were review articles. The guideline authors identified nine primary studies of the pharmacogenomics of allopurinol hypersensitivity and one meta-analysis. The recent meta-analysis of *human leukocyte antigen B (HLA-B)*5801* and allopurinol-induced Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) stated that in their literature review they found only six relevant primary studies in their database search that included MEDLINE, Pre-MEDLINE, Cochrane Library, EMBASE, International Pharmaceutical Abstracts (IPA), CINAHL, PsycINFO, the World Health Organization (WHO) International, Clinical Trial Registry, and ClinicalTrials.gov from their inceptions to June 2011. The additional three studies included in the corpus of literature include those that used a genome-wide association study (GWAS) design and were published after June 2011.

To construct an *HLA-B*58:01* minor allele frequency table based on ethnicity, allele frequency information was obtained from Allele Frequency Net Database (www.allelefrequencies.net). It is an online repository for HLA allele frequencies from both previously published and unpublished sources. All previously published data were manually checked against the original publications to verify the *HLA-B*58:01* allele frequencies. In some cases, sample sizes or allele frequencies were updated to reflect only subjects successfully genotyped for *HLA-B*58:01* (rather than the total sample size of the study) or to correct errata in the original publication. The combined analysis included 38,979 Caucasians, 5,811 Black or Africans, 882 Middle Easterners, 3,318 Hispanic or Latino and 11,531 Asians.

2015 Reaffirmation

The guideline authors searched the PubMed database (1966 to October 2014) for keywords (HLA OR HLA-B OR HLA-B58 OR HLA-B*5801) AND (allopurinol). Using these search terms, 77 publications were identified. In addition, studies annotated in PharmGKB (http://www.pharmgkb.org) were identified. Study inclusion criteria included publications that included analyses of the effect of *HLA* alleles on clinical outcomes of allopurinol use, and non-English manuscripts were excluded. Following application of these inclusion criteria, 26 publications were reviewed and included in the evidence table (Table S3 in the 2015 supplemental information [see the "Availability of Companion Documents" field]). Associations with other alleles were also collected and the positive associations found in more than one study are represented in Table S3.

To construct an *HLA-B*58:01* minor allele frequency table based on ethnicity, allele frequency information was obtained from Allele Frequency Net Database (www.allelefrequencies.net), an online repository for HLA allele frequencies from both previously published and unpublished sources. Allele frequency search/classical was carried out for *HLA-B*58:01* (accessed Dec 1st 2014).

Number of Source Documents

2013 Guideline

The guideline authors identified nine primary studies of the pharmacogenomics of allopurinol hypersensitivity and one meta-analysis.

2015 Reaffirmation

26 publications were reviewed and included in the evidence table.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was summarized into tables (see the "Availability of Companion Documents" field) and graded (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

2013 Guideline

The Clinical Pharmacogenetics Implementation Consortium's dosing recommendations are based weighing the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Three categories were chosen for recommendations: strong, moderate, optional (see the "Rating Scheme for the Strength of the Recommendations" field).

Overall, the dosing recommendations are simplified to allow rapid interpretation by clinicians.

2015 Reaffirmation

The guideline authors found no evidence that would change their original recommendations for *HLA-B*58:01* and allopurinol dosing; therefore, the original guideline publication and recommendation remain current.

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Peer Review

Description of Method of Guideline Validation

Not stated

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The evidence summarized in Supplemental Table S4 (see the "Availability of Companion Documents" field) has been graded using the slightly modified three-tiered system required by the Clinical Pharmacogenetics Implementation Consortium (see the "Rating Scheme for the Strength of the Evidence" field). Every effort was made to present evidence from high-quality studies, which provided the framework for the strength of therapeutic recommendations.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Given the high negative predictive value of the allele, especially in patients of Asian descent (>99%), *human leukocyte antigen B (HLA-B)*58:01* testing could significantly reduce the incidence and risk for allopurinol-associated severe cutaneous adverse reaction (SCAR).

Potential Harms

- As with any laboratory test, one potential risk could come from genotyping error. A false-negative genotyping result could lead to allopurinol-induced adverse events.
- Genotypes are lifelong characteristics; such errors could have a broader health implication if other associations with *human leukocyte antigen B (HLA-B)*58:01* are identified in the future.
- Several clinical factors have been reported to be associated with an increased risk for allopurinol hypersensitivity. Renal dysfunction is the most significant nongenetic factor, and patients with renal insufficiency were four times more likely to develop adverse events than those with normal renal function. The risk of allopurinol-induced hypersensitivity is also reported to increase with the concomitant use of ampicillin or amoxicillin.
- In addition to severe cutaneous adverse reaction (SCAR), allopurinol therapy is also associated with a 2%–3% incidence of less severe rashes unassociated with systemic symptoms or organ damage. Food and Drug Administration guidelines recommend discontinuing allopurinol if a rash develops.

Contraindications

Contraindications

Allopurinol is contraindicated in carriers of *human leukocyte antigen B (HLA-B)*58:01*.

Qualifying Statements

Qualifying Statements

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

- The positive predictive value for *human leukocyte antigen B (HLA-B)*58:01* is ~1.5% and the negative predictive value is 100% (based on the data from the Han-Chinese and Thai populations). Therefore, a significant number of patients carrying the allele will not develop severe cutaneous adverse reactions (SCAR) when they receive allopurinol treatment. New genetic factors may be identified in the future to differentiate the *HLA-B*58:01* carriers who are or are not likely to develop SCAR. The most severe SCAR (toxic epidermal necrolysis) carries a 30% mortality rate. However, further study is warranted on the development of SCAR in European populations.
- *HLA-B*58:01* predicts only allopurinol-induced SCAR, not other adverse events (such as mild skin rash) that a patient might experience during allopurinol treatment. The marker also does not predict the efficacy of treatment with allopurinol. Regardless of the genotyping results, physicians should monitor patients closely.

Disclaimer

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Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Hershfield MS, Callaghan JT, Tassaneeyakul W, Mushiroda T, Thorn CF, Klein TE, Lee MT. Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. Clin Pharmacol Ther. 2013 Feb;93(2):153-8. [40 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Feb (reaffirmed 2015)

Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

Source(s) of Funding

This work was funded by National Institutes of Health (NIH) grant GM61374.

Guideline Committee

Not stated

Composition of Group That Authored the Guideline

2013 Guideline

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2015 Reaffirmation

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Financial Disclosures/Conflicts of Interest

MS Hershfield is a co-inventor of pegloticase (Krystexxa) and is a consultant to, and receives royalties from, Savient Pharmaceuticals. MTM Lee is a paid consultant of YongLin Healthcare Foundation. The other authors declared no conflict of interest.

Guideline Status

This is the current release of the guideline.

The guideline developer reaffirmed this guideline in 2015.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the Pharmacogenomics Knowledgebase Web site .

Availability of Companion Documents

2013 Guideline

Supplementary material, including tables and methodological information, is available from the Pharmacogenomics Knowledgebase Web site .

In addition, an interactive dosing table is available from the Pharmacogenomics Knowledgebase Web site .

2015 Reaffirmation

The guideline update and supplemental material are available from the Pharmacogenomics Knowledgebase Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 15, 2013. The information was verified by the guideline developer on June 25, 2013. The currency of the guideline was reaffirmed by the developer in 2015 and this summary was updated by ECRI Institute on October 1, 2015.

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